PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 06 November 2000 (06.11.00)	
International application No. PCT/US99/31302	**Applicant's or agent's file reference** 00537-188W01
International filing date (day/month/year) 30 December 1999 (30.12.99)	**Priority date** (day/month/year) 31 December 1998 (31.12.98)
Applicant GORDON, Thomas, B. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

20 July 2000 (20.07.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Nestor Santesso
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

US9931302

'ATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
00537-188W01		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 99/ 31302	30/12/1999	31/12/1998
Applicant		
SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATION		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1 to 7 and 15 to 18 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula I where R4 is an optionally substituted phenyl as claimed in claims 8 to 14 and 19 and as described in examples 1 to 40.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

national Application No
PCT/US 99/31302

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/4985 A61K31/551 A61K31/5517 A61P35/00
C07D513/14 C07D519/00 //(C07D487/04,241:00,235:00),
(C07D487/04,243:00,235:00),(C07D513/14,285:00,241:00,235:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 30053 A (BIOMEASURE INC) 21 August 1997 (1997-08-21) claims 1,29; examples 7,11,13,14,17,18,20,22,24,26-29	1,15,16
E	WO 00 02881 A (SCRAS) 20 January 2000 (2000-01-20) claims 1,6	1,15,16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 July 2000	28/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/31302

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9730053 A	21-08-1997	AU 716636 B	02-03-2000
		AU 1964597 A	02-09-1997
		CA 2245823 A	21-08-1997
		CN 1216545 A	12-05-1999
		EP 0904274 A	31-03-1999
		PL 328513 A	01-02-1999
		ZA 9701254 A	14-07-1998
WO 0002881 A	20-01-2000	FR 2780974 A	14-01-2000
		AU 4622299 A	01-02-2000

YRT

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

TSAO, Y. Rocky
FISH & RICHARDSON P.C.
225 Franklin Street
Boston, MA 02110-2804
ETATS-UNIS D'AMERIQUE

RECEIVED
APR 17 2001
FISH & RICHARDSON, P.C.
BOSTON OFFICE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 09.04.2001
Applicant's or agent's file reference 00537-188WO1	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/31302	30/12/1999	31/12/1998

Applicant
SOCIETE DE CONSEILS DE RECHERCHES ET... et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

* No Docketing Required *
Reviewed By Practice Systems
Initials: YA
Reviewed By Billing Secretary
Date:

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hebert, W Tel.+49 89 2399-2152

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION ATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
00537-188WO1		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/31302	30/12/1999	31/12/1998
International Patent Classification (IPC) or national classification and IPC C07D487/00		
Applicant SOCIETE DE CONSEILS DE RECHERCHES ET... et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/07/2000	09.04.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Baston, E Telephone No. +49 89 2399 8229

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/31302

I. Basis of the rep rt

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-75	as originally filed				
Claims, No.:					
2-19	as originally filed				
1	as received on	13/01/2001	with letter of	12/01/2001	

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rul 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 16-18 "with respect to industrial applicability".

because:

   ☒ the said international application, or the said claims Nos. 16-18 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 4-14,19
	No:	Claims 1-3, 15-18
Inventive step (IS)	Yes:	Claims

	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-15,19
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

To s ction III

Claims 16-18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

To section V

The following document was cited in the search report and considered for the examination of the present application:
D1: WO 97 30053 A (BIOMEASURE INC) 21 August 1997

The present application and document D1 disclose farnesyl-transferase inhibitors using a tetrahydo-imidazo[1,2a]pyrazine basic structure.

The subject-matter of claims 1-3 and 15 is not considered novel, since D1 already discloses compounds, which fall in the scope of claim 1 (table 1, N°21 and 52).
The applicant's attention is drawn to the fact, that due to the expression "optionally substituted" any organic group is incorporated into R^{11} and thus compounds 21 and 52 of D1 are still included into claim 1 of this application.

Moreover it has to be stated, that novelty cannot be established simply by disclaiming those compounds from a claim, that are concretely disclosed in the prior art. All(!) overlapping subject-matter (compare D1, pages 64/65, claim 1) has to be excluded from claim 1 in order to establish novelty.

The subject-matter of claims 4-14 and 19 is novel (Art. 33(2) PCT), since none of the disclosed compounds is already anticipated by the prior art.

Claims 4-14 and 19 do not involve an inventive step (Art. 33(3) PCT) for the following reason:
The descripition (page 16/17) does not provide concrete inhibitory data for select congeners of the present application, which would constitute a proof of activity in the intended way.

However it has to be stated, that the prior art (D1) does not contain any indication for the introduction of heterocyclic groups in position 7 of the tetrahydroimidazo[1,2a] pyrazine structure or the preparation of imidazo[1,2c][1,4]benzodiazepines to provide novel compounds (claims 4-14) as prenyl-transferase inhibitors.

For the assessment of the present claims 16-18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

To section VI

D2: WO 00 02881 A (SCRAS) Publication date: 20 January 2000
Filing date: 05 July 1999
Priority date: 08 July 1998

This document might be relevant for the assessment of novelty and / or inventive step in the national / European phase.

IN THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

Applicant : Societe De Conseils De Recherches Et D'Applications Scientifiques S.A.
Intl. Application No.: PCT/US99/31302
Intl. Filing Date : December 30, 1999
Title: PRENYL TRANSFERASE INHIBITORS

International Preliminary Examining Authority (IPEA/US)
European Patent Office, D-80298 Munich

Attn: PCT Chapter II – E. Baston

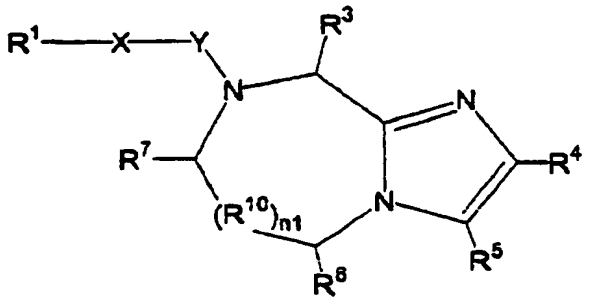
RESPONSE TO WRITTEN OPINION

The following remarks are made in response to the written opinion dated October 13, 2000 ("the Written Opinion").

In the Claims:

Please amend claim 1 as follows:

1. (Amended) A compound of formula I,



(I)

wherein

n1 is 0 or 1;

X is, independently for each occurrence, $(CHR^{11})_{n3}(CH_2)_{n4}Z(CH_2)_{n5}$,

Z is 0, $N(R^{12})$, S, or a bond;

CERTIFICATE OF TRANSMISSION BY FACSIMILE

I hereby certify that this correspondence is being transmitted by facsimile to the Patent and Trademark Office on the date indicated below.

January 12, 2001
Date of Transmission

Signature

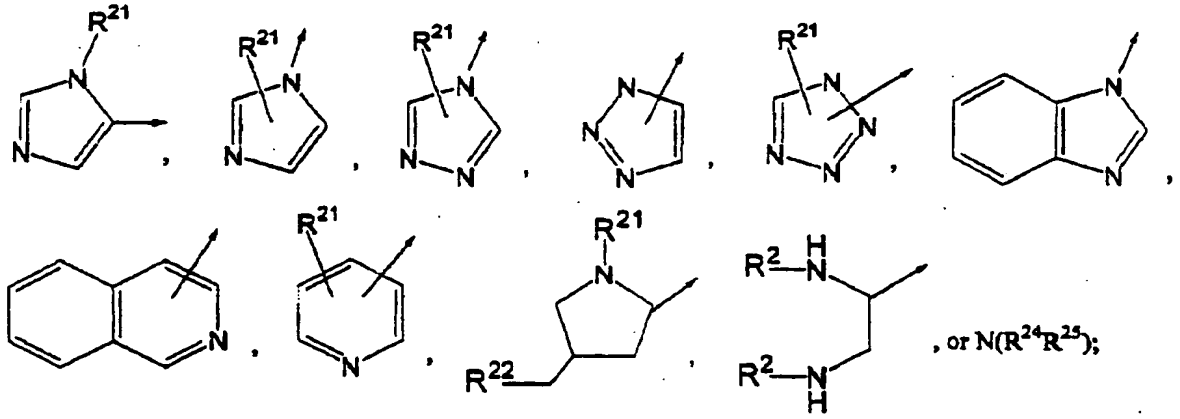
Lindsie Aldridge
Typed or Printed Name of Person Signing Certificate

n3 is, independently for each occurrence, 0 or 1;

n4 and n5 each is, independently for each occurrence, 0, 1, 2, or 3;

Y is, independently for each occurrence, CO, CH_2, CS, or a bond;

R^1 is



, or $N(R^{24}R^{25})$;

R^2, R^{11}, and R^{12} each is, independently for each occurrence, H or an optionally substituted moiety selected from the group consisting of (C_{1-6})alkyl and aryl, wherein said optionally substituted moiety is optionally substituted with one or more of R^8 or R^{30};

R^3 is, independently for each occurrence, H or an optionally substituted moiety selected from th group consisting of (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-6})cycloalkyl, (C_{3-6})cycloalkyl(C_{1-6})alkyl, (C_{5-7})cycloalkenyl, (C_{5-7})cycloalkenyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, heterocyclyl, and heterocyclyl(C_{1-6})alkyl, wherein said optionally substituted moiety is optionally substituted with one or more R^{30};

R^4 and R^5 each is, independently for each occurrence, H or an optionally substituted moiety selected from the group consisting of (C_{1-6})alkyl, (C_{3-6})cycloalkyl, aryl, and heterocyclyl, wherein said optionally substituted moiety is optionally substituted with one or more R^{30}, wherein each said substituent is independently selected, or R^4 and R^5 can be taken together with the carbons to which they are attached to form aryl;

R^6 is, independently for each occurrence, H or an optionally substituted moiety selected from the group consisting of (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{3-6})cycloalkyl, (C_{3-6})cycloalkyl(C_{1-6})alkyl, (C_{5-7})cycloalkenyl, (C_{5-7})cycloalkenyl(C_{1-6})aikyl, aryl, aryl(C_{1-6})alkyl, heterocyclyl, and heterocyclyl(C_{1-6})alkyl, wherein said optionally substituted moiety is optionally substituted with

one or more substituents each independently selected from the group consisting of OH, (C_{1-6})alkyl, (C_{1-6})alkoxy, -N(R^8R^9), -COOH, -CON(R^8R^9), and halo,

where R^8 and R^9 each is, independently for each occurrence, H, (C_{1-6})alkyl, (C_{1-6})alkenyl, (C_{2-6})alkynyl, aryl, or aryl(C_{1-6})alkyl;

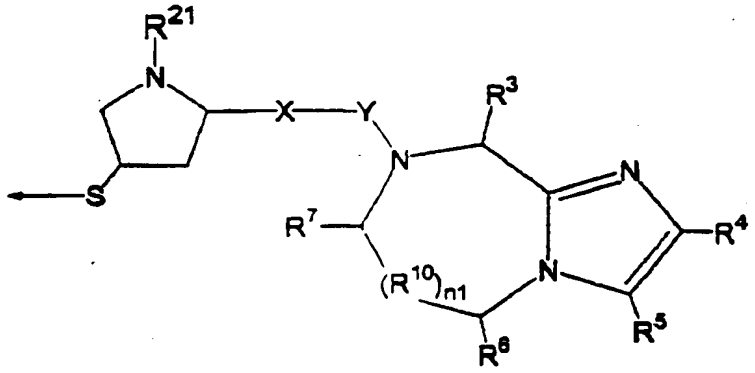
R^7 is, independently for each occurrence, H, =O, =S, or an optionally substituted moiety selected from the group consisting of (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{3-6},)cycloalkyl, (C_{3-6})cycloalkyl(C_{1-6})alkyl, (C_{5-7})cycloalkenyl,(C_{5-7})cycloalkenyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, heterocyclyl, and heterocyclyl(C_{1-6})alkyl, wherein said 25 optionally substituted moiety is optionally substituted with one or more substituents each independently selected from the group consisting of OH, (C_{1-6})alkyl, (C_{1-6})alkoxy, -N(R^8R^9), -COOH, -CON(R^8R^9), and halo;

R^{10} is C;

or when nl =0, R^6 and R^7 can be taken together with the carbon atoms to which they are attached to form aryl or cyclohexyl;

R^{21} is, independently for each occurrence, H or an optionally substituted moiety selected from the group consisting of (C_{1-6})alkyl and aryl(C_{1-6})alkyl, wherein said optionally substituted moiety is optionally substituted with one or more substituents each independently selected from the group consisting of R^8 and R^{30};

R^{22} is H, (C_{1-6})alkylthio, (C_{3-6})cycloalkylthio, R^8—CO-, or a substituent according to the formula



R^{24} and R^{25} each is, independently for each occurrence, H, (C_{1-6})alkyl, or aryl(C_{1-6})alkyl;

R^{30} is, independently for each occurrence, (C_{1-6})alkyl, -O-R^8, -S(O)$_{n6}R^8$, -S(O)$_{n7}$N(R^8R^9),

-N(R^8R^9), -CN, -NO_2, -CO_2, R^8, -CON(R^8R^9), -NCO-R^8, or halogen;

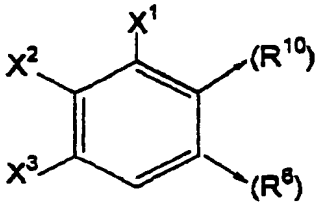
n6 and n7 each is, independently for each occurrence, 0, 1, or 2;

wherein said heterocyclyl is azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothio-pyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, Z-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyridyl N-oxide, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydro-quinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, or thienyl; and

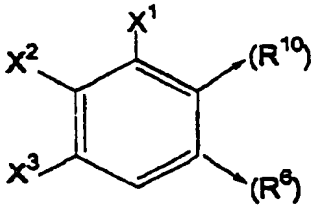
wherein said aryl is phenyl or naphthyl;

provided that:

when nl =1, R^{10} is C and R^6 is H, then R^{10} and R^7 can be taken together to form

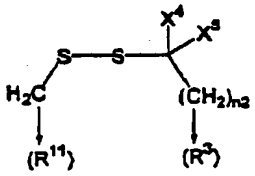


; or when nl =1, R^{10} is C, and R^7 is =O, -H, or =S, then R^{10} and R^6 can be taken together to form



wherein X^1, X^2, and X^3 each is, independently, H, halogen, -NO_2, -NCO-R^8, -CO_2R^8, -CN, or -CON(R^8R^9); and

when $R^1$is N($R^{24}R^{25}$), then n3 is 1, n4 and n5 each is 0, Z is a bond, and R^3 and R^{11} can be taken together to form



wherein n2 is 1-6, and X^4 and X^5 each is, independently, H, (C_{1-6})alkyl, or aryl, or X^4 and X^5 can be taken together to form (C_{3-6})cycloalkyl;

or a pharmaceutically acceptable salt thereof;

with the proviso that the compound of formula I is not:

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-phenyl-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(4-fluorophenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(2-methoxy-phenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(3-methoxy-phenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(4-methoxy-phenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;

7-(2-amino-1-oxo-3-thio-propyl)-8-(2-hydroxy-ethyl)-2-phenv-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;

7-(2-amino-3-thio-propyl)-8-butyl-3-phenyl-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;

7-(2-amino-1-oxo-3-thio-propyl-2-(2-methoxyphenyl-8-(2-methylpropyl)-5,6,7,8-tetrahydro-imidazo [1, 2a] pyrazine;

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(2-ethoxyphenyl)-5,6,7,8-tetrahydro-imidazo-[1, 2a]-pyrazine;

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(2-hydroxyphenyl)-5,6,7,8-tetrahydro-imidazo-[1, 2a]-pyrazine;

7-(2-amino-1-oxo-3-thiopropyl)-8-(2-methylpropyl)-2-(1-naphthyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;

7-(2-amino-1-oxo-3-thiopropyl)-8-(1-methylpropyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1, 2a]pyrazine;

bis-1, 1 '-7-(2-amino-1-oxo-3-thiopropyl -(2-(1-naphthyl)-8-(2-methylpropyl)-5,6,7,8-tetrahydroimidazo [1, 2a] pyrazin-7-yl)disulfide;

bis-1, 1 '-[7-(2-amino-1-oxo-3-thiopropyl)-2-(methoxyphenyl)-8-(1-methylpropyl)-5,6,7,8-tetrahydroimidazo [1, 2a] pyrazine] disulfide;

7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2-(2-methylphenyl)-5,6,7,8-tetrahydroimidazo[1, 2a]

pyrazine;
bis-1, 1' -[7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2-(2-methylphenyl)-5,6,7,8-tetrahydroimidazo [1, 2a] pyrazine disulfide;
7-(2-amino-1-oxo-3-thiopropyl)-8-(1,1-dimethylethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-8-(1 methylpropyl)-2-(2-(phenylmethoxy)phenyl)-5,6,7,8-tetrahydroimidazo[1, 2a]pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylmethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(1-methylethyl)-5,6,7,8-tetrahydroimidazo [1, 2a] pyrazine;
bis-1, 1'-[7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(1-methylethyl)-5,6,7,8-tetrahydroimidazo [1, 2a] pyrazine] disulfide;
7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2(2-hydroxy-6-methoxyphenyl)-5,6,7,8-tetrahydro [1,2a] pyrazine;
bis-1, 1' -[1, 7-(12-amino-1-oxo-3-thiopropyl)-8-(1, 1-dimethylethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1, 2a] pyrazine] disulfide;
bis-1, 1'-[2-amino-3-(8-butyl-2-cyclohexyl-5,6,7,8-tetrahydro-imidazo-[1,2a] pyrazin-7-yl)-3-oxo-propyl] disulfide;
7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2,3-diphenyl-5,6,7,8 tetrahydroimidazo-[1,2a] pyrazine;
bis-1, 1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2,3-diphenyl-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine] disulfide;
bis-1, 1 '-[7-(2-amino-1-oxo-3-thiopropyl)-8-(1-methylpropyl)-2-(2-(phenylmethoxy) phenyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine] disulfide;
bis-1, 1'-[2-amino-3-(2-cyclohexyl-8-(cyclohexylmethyl)-5,6,7,8-tetrahydroimidazo [1, 2a] pyrazin-7-yl)-3-oxo-propyl] disulfide;
bis-1, 1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylmethyl)-2-(2_methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine]disulfide;
bis-1, 1 '-[7-(2-amino-1-oxo-3-thiopropyl)-8-hexyl-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine] disulfide;
7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylethyl)-2-(2-methoxyphenyl)-5,6,7,8-

tetrahydroimidazo [1,2a] pyrazine;
bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine] disulfide;
7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1, 2a] pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-8-(2-(4-methoxycyclohexyl)-methyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine;
bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine] disulfide;
7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylmethyl)-2-phenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;
bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(2-(4-methoxycyclohexyl)-methyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1, 2a] pyrazine] disulfide;
7-(2-amino-1-oxo-3-thiopropyl)-8-(4-methoxycyclohexyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine;
[S-(2-amino-3-oxo-3-(8-cyclohexylmethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydro-imidazo [1, 2a] pyrazin-7-yl)-propyl]-S'-cyclohexyldisulfide;
7-(2-amino-1-oxo-3-thiopropyl)-8-(4-methoxycyclohexyl) methyl-2-(2-methoxyphenyl)-5,6,7,8-terahydroimidazo [1, 2a] pyrazine (cis isomer);
7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(4-piperidinylmethyl)-5,6,7,8-terahydroimidazo [1,2a] pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(2-piperidinylmethyl)-5,6,7,8-terahydroimidazo [1, 2a] pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(3-piperidinylmethyl)-5,6,7,8-tetrahydroimidazol [1, 2a] pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylmethyl)-2-(1-naphthyl)-5,6,7,8-tetrahydroimidazo [1, 2a] pyrazine;
[S-[2-amino-3-oxo-3-(8-cyclohexylmethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydro-imidazo [1, 2a] pyrazin-7-yl)-propyl]-S'-ethyl] disulfide;
7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(2-methylthio)-ethyl-5,6,7,8-tetrahydroimidazo [1, 2a] pyrazine;

7-(2-amino-1-oxo-3-thiopropyl)-8-(3-indolinylmethyl)-2-(2-methoxyphenyl)-8-5,6,7,8-tetrahydroimidazo [], 2a] pyrazine;

7-(2-amino-I-oxo-3-thiopropyl)-8-(1-methylimidazol-3-yl) methyl-2-(2-methoxyphenyl)-8-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine;

7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(2-phenoxyethyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine; and

bis-1,1'-[2-amino-3-(2-(2-methoxyphnenyl)-8-(2-phenoxyethyl)-5,6,7,8-tetrahydro-imidazo [], 2a] pyrazin-7-yl)-3-oxopropyl]-disulfide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
00537-188WO1		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/31302	30/12/1999	31/12/1998
International Patent Classification (IPC) or national classification and IPC C07D487/00		
Applicant SOCIETE DE CONSEILS DE RECHERCHES ET... et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/07/2000	09.04.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Baston, E Telephone No. +49 89 2399 8229

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/31302

I. Basis of th r port

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-75	as originally filed				

Claims, No.:

2-19	as originally filed				
1	as received on	13/01/2001	with letter of	12/01/2001	

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of: —

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 16-18 "with respect to industrial applicability".

because:

   ☒ the said international application, or the said claims Nos. 16-18 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4-14,19
	No:	Claims	1-3, 15-18
Inventive step (IS)	Yes:	Claims	

	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-15,19
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

To s ction III

Claims 16-18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

To section V

The following document was cited in the search report and considered for the examination of the present application:
D1: WO 97 30053 A (BIOMEASURE INC) 21 August 1997

The present application and document D1 disclose farnesyl-transferase inhibitors using a tetrahydo-imidazo[1,2a]pyrazine basic structure.

The subject-matter of claims 1-3 and 15 is not considered novel, since D1 already discloses compounds, which fall in the scope of claim 1 (table 1, N°21 and 52).
The applicant's attention is drawn to the fact, that due to the expression "optionally substituted" any organic group is incorporated into R^{11} and thus compounds 21 and 52 of D1 are still included into claim 1 of this application.

Moreover it has to be stated, that novelty cannot be established simply by disclaiming those compounds from a claim, that are concretely disclosed in the prior art. All(!) overlapping subject-matter (compare D1, pages 64/65, claim 1) has to be excluded from claim 1 in order to establish novelty.

The subject-matter of claims 4-14 and 19 is novel (Art. 33(2) PCT), since none of the disclosed compounds is already anticipated by the prior art.

Claims 4-14 and 19 do not involve an inventive step (Art. 33(3) PCT) for the following reason:
The descripition (page 16/17) does not provide concrete inhibitory data for select congeners of the present application, which would constitute a proof of activity in the intended way.

However it has to be stated, that the prior art (D1) does not contain any indication for the introduction of heterocyclic groups in position 7 of the tetrahydroimidazo[1,2a] pyrazine structure or the preparation of imidazo[1,2c][1,4]benzodiazepines to provide novel compounds (claims 4-14) as prenyl-transferase inhibitors.

For the assessment of the present claims 16-18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

To section VI

D2: WO 00 02881 A (SCRAS) Publication date: 20 January 2000
Filing date: 05 July 1999
Priority date: 08 July 1998

This document might be relevant for the assessment of novelty and / or inventive step in the national / European phase.

IN THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

Applicant : Societe De Conseils De Recherches Et D'Applications Scientifiques S.A.
Intl. Application No.: PCT/US99/31302
Intl. Filing Date : December 30, 1999
Title: PRENYL TRANSFERASE INHIBITORS

International Preliminary Examining Authority (IPEA/US)
European Patent Office, D-80298 Munich

Attn: PCT Chapter II – E. Baston

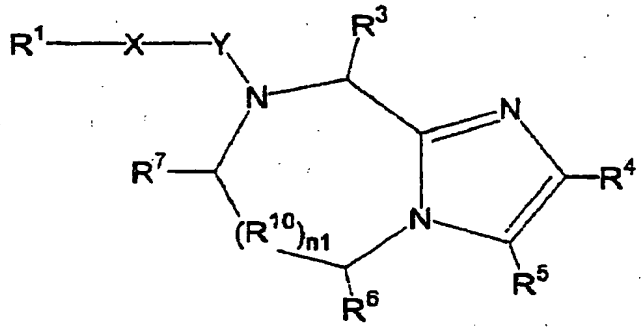
RESPONSE TO WRITTEN OPINION

The following remarks are made in response to the written opinion dated October 13, 2000 ("the Written Opinion").

In the Claims:

Please amend claim 1 as follows:

1. (Amended) A compound of formula I,



(I)

wherein

nl is 0 or 1;

X is, independently for each occurrence, $(CHR^{11})_{n3}(CH_2)_{n4}Z(CH_2)_{n5}$,

Z is 0, $N(R^{12})$, S, or a bond;

CERTIFICATE OF TRANSMISSION BY FACSIMILE

I hereby certify that this correspondence is being transmitted by facsimile to the Patent and Trademark Office on the date indicated below.

January 12, 2001
Date of Transmission

Signature

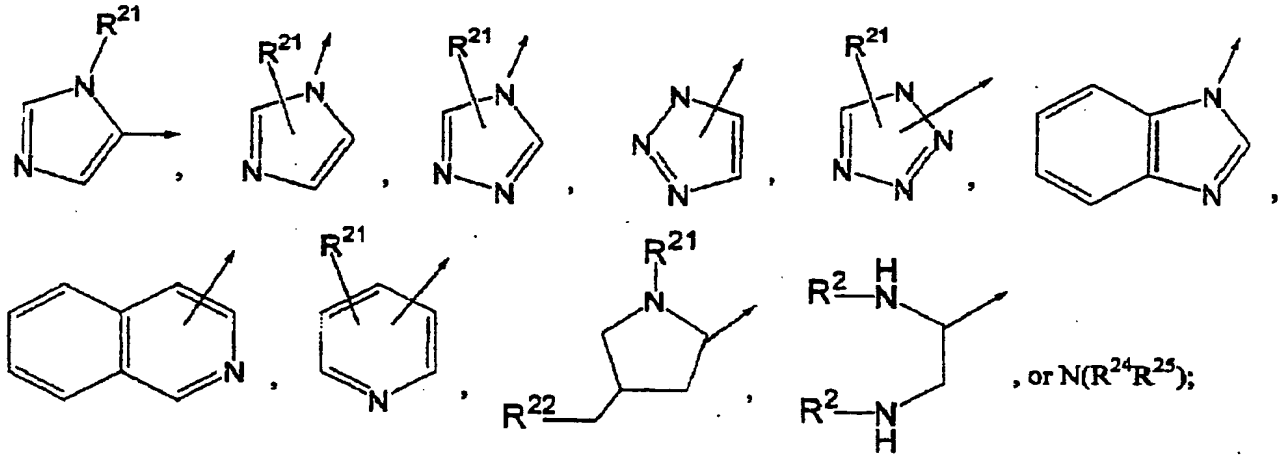
Lindsie Aldridge
Typed or Printed Name of Person Signing Certificate

n3 is, independently for each occurrence, 0 or 1;

n4 and n5 each is, independently for each occurrence, 0, 1, 2, or 3;

Y is, independently for each occurrence, CO, CH_2, CS, or a bond;

R^1 is



, or $N(R^{24}R^{25})$;

R^2, R^{11}, and R^{12} each is, independently for each occurrence, H or an optionally substituted moiety selected from the group consisting of (C_{1-6})alkyl and aryl, wherein said optionally substituted moiety is optionally substituted with one or more of R^8 or R^{30};

R^3 is, independently for each occurrence, H or an optionally substituted moiety selected from the group consisting of (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-6})cycloalkyl, (C_{3-6})cycloalkyl(C_{1-6})alkyl, (C_{5-7})cycloalkenyl, (C_{5-7})cycloalkenyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, heterocyclyl, and heterocyclyl(C_{1-6})alkyl, wherein said optionally substituted moiety is optionally substituted with one or more R^{30};

R^4 and R^5 each is, independently for each occurrence, H or an optionally substituted moiety selected from the group consisting of (C_{1-6})alkyl, (C_{3-6})cycloalkyl, aryl, and heterocyclyl, wherein said optionally substituted moiety is optionally substituted with one or more R^{30}, wherein each said substituent is independently selected, or R^4 and R^5 can be taken together with the carbons to which they are attached to form aryl;

R^6 is, independently for each occurrence, H or an optionally substituted moiety selected from the group consisting of (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{3-6})cycloalkyl, (C_{3-6})cycloalkyl(C_{1-6})alkyl, (C_{5-7})cycloalkenyl, (C_{5-7})cycloalkenyl(C_{1-6})aikyl, aryl, aryl(C_{1-6})alkyl, heterocyclyl, and heterocyclyl(C_{1-6})alkyl, wherein said optionally substituted moiety is optionally substituted with

one or more substituents each independently selected from the group consisting of OH, (C_{1-6})alkyl, (C_{1-6})alkoxy, -N(R^8R^9), -COOH, -CON(R^8R^9), and halo,

where R^8 and R^9 each is, independently for each occurrence, H, (C_{1-6})alkyl, (C_{1-6})alkenyl, (C_{2-6})alkynyl, aryl, or aryl(C_{1-6})alkyl;

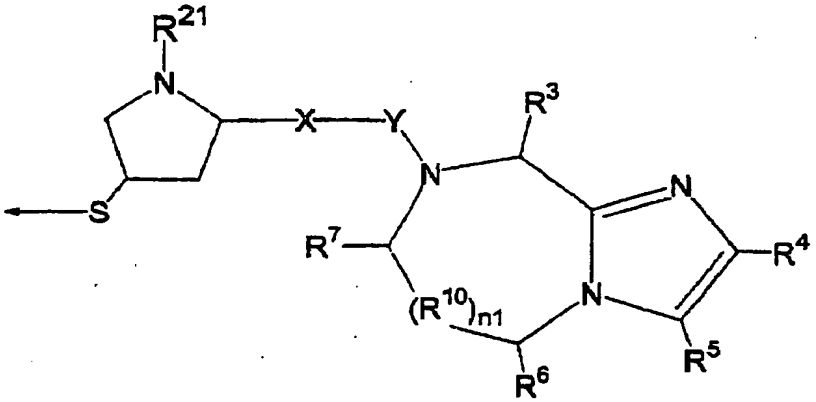
R^7 is, independently for each occurrence, H, =O, =S, or an optionally substituted moiety selected from the group consisting of (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{3-6},)cycloalkyl, (C_{3-6})cycloalkyl(C_{1-6})alkyl, (C_{5-7})cycloalkenyl,(C_{5-7})cycloalkenyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, heterocyclyl, and heterocyclyl(C_{1-6})alkyl, wherein said 25 optionally substituted moiety is optionally substituted with one or more substituents each independently selected from the group consisting of OH, (C_{1-6})alkyl, (C_{1-6})alkoxy, -N(R^8R^9), -COOH, -CON(R^8R^9), and halo;

R^{10} is C;

or when nl =0, R^6 and R^7 can be taken together with the carbon atoms to which they are attached to form aryl or cyclohexyl;

R^{21} is, independently for each occurrence, H or an optionally substituted moiety selected from the group consisting of (C_{1-6})alkyl and aryl(C_{1-6})alkyl, wherein said optionally substituted moiety is optionally substituted with one or more substituents each independently selected from the group consisting of R^8 and R^{30};

R^{22} is H, (C_{1-6})alkylthio, (C_{3-6})cycloalkylthio, R^8—CO-, or a substituent according to the formula



R^{24} and R^{25} each is, independently for each occurrence, H, (C_{1-6})alkyl, or aryl(C_{1-6})alkyl;

R^{30} is, independently for each occurrence, (C_{1-6})alkyl, -O-R^8, -S(O)$_{n6}R^8$, -S(O)$_{n7}$N(R^8R^9),

-N(R^8R^9), -CN, -NO_2, -CO_2, R^8, -CON(R^8R^9), -NCO-R^8, or halogen;

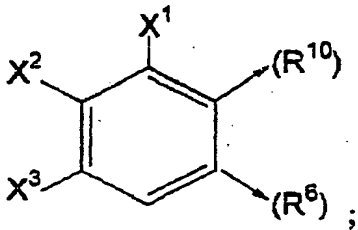
n6 and n7 each is, independently for each occurrence, 0, 1, or 2;

wherein said heterocyclyl is azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothio-pyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, Z-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyridyl N-oxide, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydro-quinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, or thienyl; and

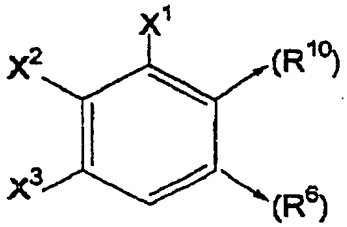
wherein said aryl is phenyl or naphthyl;

provided that:

when nl =1, R^{10} is C and R^6 is H, then R^{10} and R^7 can be taken together to form

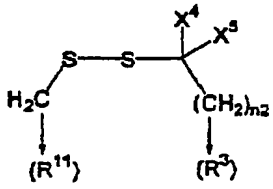


; or when nl =1, R^{10} is C, and R^7 is =0, -H, or =S, then R^{10} and R^6 can be taken together to form



wherein X^1, X^2, and X^3 each is, independently, H, halogen, -NO_2, -NCO-R^8, -CO_2R^8, -CN, or -CON(R^8R^9); and

when $R^1$is N($R^{24}R^{25}$), then n3 is 1, n4 and n5 each is 0, Z is a bond, and R^3 and R^{11} can be taken together to form



wherein n2 is 1-6, and X^4 and X^5 each is, independently, H, (C_{1-6})alkyl, or aryl, or X^4 and X^5 can be taken together to form (C_{3-6})cycloalkyl;

or a pharmaceutically acceptable salt thereof;

with the proviso that the compound of formula I is not:

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-phenyl-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(4-fluorophenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(2-methoxy-phenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(3-methoxy-phenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(4-methoxy-phenyl)-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;

7-(2-amino-1-oxo-3-thio-propyl)-8-(2-hydroxy-ethyl)-2-pheny-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;

7-(2-amino-3-thio-propyl)-8-butyl-3-phenyl-5,6,7,8-tetrahydro-imidazo-[1,2a]-pyrazine;

7-(2-amino-1-oxo-3-thio-propyl-2-(2-methoxyphenyl-8-(2-methylpropyl)-5,6,7,8-tetrahydro-imidazo [1, 2a] pyrazine;

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(2-ethoxyphenyl)-5,6,7,8-tetrahydro-imidazo-[1, 2a]-pyrazine;

7-(2-amino-1-oxo-3-thio-propyl)-8-butyl-2-(2-hydroxyphenyl)-5,6,7,8-tetrahydro-imidazo-[1, 2a]-pyrazine;

7-(2-amino-1-oxo-3-thiopropyl)-8-(2-methylpropyl)-2-(1-naphthyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;

7-(2-amino-1-oxo-3-thiopropyl)-8-(1-methylpropyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1, 2a]pyrazine;

bis-1, 1 '-7-(2-amino-1-oxo-3-thiopropyl -(2-(1-naphthyl)-8-(2-methylpropyl)-5,6,7,8-tetrahydroimidazo [1, 2a] pyrazin-7-yl)disulfide;

bis-1, 1 '-[7-(2-amino-1-oxo-3-thiopropyl)-2-(methoxyphenyl)-8-(1-methylpropyl)-5,6,7,8-tetrahydroimidazo [1, 2a] pyrazine] disulfide;

7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2-(2-methylphenyl)-5,6,7,8-tetrahydroimidazo[1, 2a]

pyrazine;
bis-1, 1' -[7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2-(2-methylphenyl)-5,6,7,8-tetrahydroimidazo [l, 2a] pyrazine disulfide;
7-(2-amino-1-oxo-3-thiopropyl)-8-(1,1-dimethylethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-8-(l methylpropyl)-2-(2-(phenylmethoxy)phenyl)-5,6,7,8-tetrahydroimidazo[l, 2a]pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylmethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(1-methylethyl)-5,6,7,8-tetrahydroimidazo [l, 2a] pyrazine;
bis-1, 1'-[7-(2-amino-l-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(1-methylethyl)-5,6,7,8-tetrahydroimidazo [l, 2a] pyrazine] disulfide;
7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2(2-hydroxy-6-methoxyphenyl)-5,6,7,8-tetrahydro [1,2a] pyrazine;
bis-1, 1' -[1, 7-(12-amino-1-oxo-3-thiopropyl)-8-(l, 1-dimethylethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [l, 2a] pyrazine] disulfide;
bis-1, 1'-[2-amino-3-(8-butyl-2-cyclohexyl-5,6,7,8-tetrahydro-imidazo-[1,2a] pyrazin-7-yl)-3-oxo-propyl] disulfide;
7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2,3-diphenyl-5,6,7,8 tetrahydroimidazo-[1,2a] pyrazine;
bis-1, 1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-butyl-2,3-diphenyl-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine] disulfide;
bis-1, 1 '-[7-(2-amino-1-oxo-3-thiopropyl)-8-(1-methylpropyl)-2-(2-(phenylmethoxy) phenyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine] disulfide;
bis-l, l'-[2-amino-3-(2-cyclohexyl-8-(cyclohexylmethyl)-5,6,7,8-tetrahydroimidazo [l, 2a] pyrazin-7-yl)-3-oxo-propyl] disulfide;
bis-l, l'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylmethyl)-2-(2_methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine]disulfide;
bis-1, 1 '-[7-(2-amino-1-oxo-3-thiopropyl)-8-hexyl-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine] disulfide;
7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylethyl)-2-(2-methoxyphenyl)-5,6,7,8-

tetrahydroimidazo [1,2a] pyrazine;
bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine] disulfide;
7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1, 2a] pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-8-(2-(4-methoxycyclohexyl)-methyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine;
bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine] disulfide;
7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylmethyl)-2-phenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;
bis-1,1'-[7-(2-amino-1-oxo-3-thiopropyl)-8-(2-(4-methoxycyclohexyl)-methyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1, 2a] pyrazine] disulfide;
7-(2-amino-1-oxo-3-thiopropyl)-8-(4-methoxycyclohexyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine;
[S-(2-amino-3-oxo-3-(8-cyclohexylmethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydro-imidazo [1, 2a] pyrazin-7-yl)-propyl]-S'-cyclohexylldisulfide;
7-(2-amino-1-oxo-3-thiopropyl)-8-(4-methoxycyciohexyl) methyl-2-(2-methoxyphenyl)-5,6,7,8-terahydroimidazo [1, 2a] pyrazine (cis isomer);
7-(2-amino-l-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(4-piperidinylmethyl)-5,6,7,8-terahydroimidazo [1,2a] pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(2-piperidinylmethyl)-5,6,7,8-terahydroimidazo [1, 2a] pyrazine;
7-(2-amino-l-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(3-piperidinylmethyl)-5,6,7,8-tetrahydroimidazol [1, 2a] pyrazine;
7-(2-amino-1-oxo-3-thiopropyl)-8-(cyclohexylmethyl)-2-(1-naphthyl)-5,6,7,8-tetrahydroimidazo [1, 2a] pyrazine;
[S-[2-amino-3-oxo-3-(8-cyclohexylmethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydro-imidazo [1, 2a] pyrazin-7-y1)-propyl]-S'-ethyl] disulfide;
7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(2-methylthio)-ethyl-5,6,7,8-tetrahydroimidazo [1, 2a] pyrazine;

7-(2-amino-1-oxo-3-thiopropyl)-8-(3-indolinylmethyl)-2-(2-methoxyphenyl)-8-5,6,7,8-tetrahydroimidazo [1, 2a] pyrazine;

7-(2-amino-I-oxo-3-thiopropyl)-8-(1-methylimidazol-3-yl) methyl-2-(2-methoxyphenyl)-8-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine;

7-(2-amino-1-oxo-3-thiopropyl)-2-(2-methoxyphenyl)-8-(2-phenoxyethyl)-5,6,7,8-tetrahydroimidazo [1,2a] pyrazine; and

bis-1,1'-[2-amino-3-(2-(2-methoxyphnenyl)-8-(2-phenoxyethyl)-5,6,7,8-tetrahydro-imidazo [1, 2a] pyrazin-7-yl)-3-oxopropyl]-disulfide.

PATENT COOPERATION TRE

4R+

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

FISH & RICHARDSON P.C.
Attn. TSAO, Y. Rocky
225 Franklin Street
Boston, Massachusetts 02110-2804
UNITED STATES OF AMERICA

Docketed By Billing Secretar
Due Date: ____
Deadline: ____
Initials: ____

RECEIVED
AUG 0 2 2000
FISH & RICHARDSON, P.C.
BOSTON OFFICE

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing (*day/month/year*) 28/07/2000
Applicant's or agent's file reference 00537-188W01	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 99/31302	International filing date (*day/month/year*) 30/12/1999
Applicant SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATION	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

Docketed Practice Systems
RESP TO RPT 9/28/00
Art (001) 10/28/00
Initials: LXA
Record: ____

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	John De Bruijn

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TRE

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
00537-188W01		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 99/ 31302	30/12/1999	31/12/1998
Applicant		
SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATION		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. -

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

International Application No
PCT/US 99/31302

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/4985 A61K31/551 A61K31/5517 A61P35/00
C07D513/14 C07D519/00 //(C07D487/04,241:00,235:00),
(C07D487/04,243:00,235:00),(C07D513/14,285:00,241:00,235:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 30053 A (BIOMEASURE INC) 21 August 1997 (1997-08-21) claims 1,29; examples 7,11,13,14,17,18,20,22,24,26-29	1,15,16
E	WO 00 02881 A (SCRAS) 20 January 2000 (2000-01-20) claims 1,6	1,15,16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 July 2000	28/07/2000

Name and mailing address of the ISA	Authorized officer
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1 to 7 and 15 to 18 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds
of formula I where R4 is an optionally substituted phenyl as claimed in claims 8 to 14 and 19 and as described in examples 1 to 40.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/31302

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 16 to 18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU 1964597 A	02-09-1997
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		CN 1216545 A	12-05-1999
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